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(54) Title: CONTROLLED RELEASE POTASSIUM CHLORIDE PELLET BASED PHARMACEUTICAL COMPOSITIONS HAVING A HIGH ACTIVE INGREDIENT CONTENT

(57) Abstract

The invention relates to controlled release multi–dosage pharmaceutical composition in solid oral form, preferably in the form of tablets or hard gelatine capsules and having a potassium chloride content of 500–1000 mg per dosage unit characterized by a content of at least 70 % by weight of potassium chloride, in the form of coated or partially uncoated pellets. The tablets or hard gelatine capsules according to the present invention are comprising pellets which contain at least 70 % by weight of potassium chloride, 10–25 % by weight of microcrystalline cellulose, 0.1–0.5 % by weight of an anti–adhesion agent and 0.1–5.0 % by weight of a hydrophobizing agent; a coating layer applied onto said pellets comprising 3–10 % by weight of an ethyl acrylate/methyl methacrylate copolymer and/or an ammonium methacrylate copolymer, a hydrophobizing agent, talc and optionally a dye; and optionally potassium chloride particles and further auxiliary agents applied onto said layer.

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Controlled release potassium chloride pellet based pharmaceutical compositions having a high active ingredient content

Background of the invention

The invention relates to controlled release potassium chloride pellet based pharmaceutical compositions having a high active ingredient content and a process for the preparation thereof. The pharmaceutical composition of the present invention contains 500-1000 mg (6.7-13.4 milliequiv. K^+) of potassium chloride per dosage unit in the form of coated and partly coated pellets.

The term "pellet" relates to substantially spherical particles.

State of the prior art

Potassium chloride has been widespreadly used for a long time in therapy for the treatment of hypochalaemia (potassium deficiency) of various origins. In medical practice potassium chloride is used orally and in characteristic high doses (1-6 g per day) [e.g. Pharmindex kompendium (1995), MediMedia Információs Kft.; Knoll, J.: Gyógyszertan, Medicina könyvkiadó, Budapest, (1983); Gyógyszer Vademecum (1996), Volume I, pages 706-708, Országos Gyógyszerészeti Intézet, Budapest, (1996).]

According to the most general and eldest method potassium is introduced into the living organism by preparing an aqueous solution from an easily soluble tablet obtained

from a readily soluble potassium salt with the aid of auxiliary agent and giving said solution to drink to the patient.

In case of more up-to-date compositions the dissolution of the tablet is facilitated by preparing a so-called effervescent tablet. If such compositions are used, the uniform administration of the potassium ions depends on the reliability of the handling personnel, and the cooperation of the patient.

The aim of so-called sustained release (retarded) compositions is to provide potassium ions gradually and continuously for the organism, i.e. to ensure sustained release of the active ingredient within a period of 6-10 hours.

The most simple way of preparing retarded compositions is the following: tablet/dragée cores containing potassium chloride are prepared and coated with a layer providing sustained release (e.g. Hungarian patent No. 194,495 or United Kingdom patent No. 1,340,921).

Another approach is the so-called matrix tablet. Potassium chloride is included with the aid of natural or artificial shell-forming materials and the release of the active ingredient takes place by dissolution of the salt in the shell system and diffusion thereof. After dissolution of the active ingredient the insoluble spongy shell-system may remain back and cause undesired side effects.

The disadvantage of such so-called "mono-dosage" compositions is that the tablet may adhere to the wall of the gastrointestinal system and the high local concentration of the released potassium may cause bleeding and ulcer in serious

cases [see e.g. Issekutz: Gyógyszerrendelés, Medicina, Budapest, (1975), page 461]. Sugar coated dragées containing a wax matrix (not enterosolvent) were marketed as slow active ingredient release compositions. According to "Physicians Desk Reference", Medical Economics Co. Inc., N.Y., 794, (1979) in case of wax matrix compositions less intestinal lesions were observed than when using enterosolvent potassium chloride compositions but bleeding in the upper gastrointestinal system was observed with this type of compositions too. In US patent No. 4,235,870 the preparation of matrix tablets containing fatty alcohols and hydrated hydroxyalkyl cellulose ethers in a ratio of 2:1 - 4:1 is described; potassium chloride is released from such matrix tablets within 5-10 hours after oral administration. The disadvantage of said matrix tablets is that the composition does not disintegrate but remains in one piece and this may cause high potassium chloride concentration in the gastrointestinal tract.

Hungarian patent No. 191,426 relates to the preparation of sustained release potassium chloride tablets containing a hydrophobic polymer (polyvinyl butyral). This composition has several drawbacks. On the one hand high local potassium chloride concentration is formed, while on the other in case of elder patients having a slower peristaltic motion after release of the active ingredient the residual spongy matrix leaves the intestines only difficultly; this occurs particularly if a large number of tablets is administered.

The most up-to-date form of pharmaceutical compositions are the so-called multi-dose compositions whereby many (several hundred or thousand) tiny dosage units are filled into a capsule or pressed into quickly disintegrating tablets.

The above composition form shows the following advantages:

– The release of the active ingredient takes place separated in time and - due to the many tiny particles - also in space and thus an undesired high local potassium chloride concentration, which may cause harmful side effects, can be avoided.

– The distribution of residence in time of the multi-dose compositions in the gastrointestinal tract is more favourable (sustained) than that of mono-dose compositions.

– The capsule may be opened, if desired, and the poured-out particles may be administered by admixture with food or liquids.

The known multi-dose potassium chloride compositions are generally prepared by coating crude crystals with a layer, thus delaying the release of the active ingredient and the dissolution of the salt (see e.g. Hungarian patent No. 191,102 or WO 86/04817).

Since the preparation of such compositions requires the use of raw materials of adequate purity, purification of potassium chloride is needed. This is generally carried out by means of recrystallization which causes a decrease of the

particle size, i.e. the preparation of crude granular crystals is circumstantial and expensive.

The particle size of commercially available special crude granular potassium chloride crystals is generally 0.3-0.5 mm and the specific surface thereof amounts to about 10-6 m^2/kg [the actual density is 1.984 g/cm^3; see Römpp Vegyészeti lexikon, Műszaki könyvkiadó, Budapest, (1982)]. This means that in order to achieve a suitably high release velocity, a large amount (about 10-30 % by weight) of coating material is to be applied onto the surface of the crystals (see e.g. European patent No. 052,075). Potassium chloride crystals prepared in great quantities generally have a much lower particle size (consequently a much higher specific surface) and therefore the preparation of sustained release compositions requires an unacceptably high amount of coating agent. Said high amount of coating agent makes the step of coating technically difficult to be carried out and the coated particles are susceptible to adhesion and for this reason special measures are to be taken to avoid sticking of the particles.

According to US patent No. 4,259,315 potassium chloride crystals having an average particle size of about 0.4 mm are coated by means of a microencapsulating process using ethyl cellulose in cyclohexane as medium (said process is described in US patent No. 3,415,758), whereupon 0.05--5.0 % by weight of a substance having a HLB value higher than 10 (i.e. a hydrophilic surfactant) is added in order to ensure uniform distribution of the microcapsules filled into the

hard gelatine capsule in the digesting juice. Due to the relatively small particle size of crystalline potassium chloride the amount of the coating must be about 20 % by weight and in the course of the microencapsulating process a large amount of cyclohexane is to be used which involves the risk of environmental pollution.

According to WO 86/04817 potassium chloride crystals having a particle size of about 0.3-0.5 mm are coated by a fluidization spraying procedure by using a 3:1 - 30:1 by weight mixture of ethyl cellulose and hydroxypropyl cellulose in a solution formed with a mixture of chloroform and ethanol. The required amount of the coating material is 9.5-18 % by weight. The coated crystals are admixed with conventional tabletting auxiliary agents to give quickly disintegrating tablets which yield in the gastrointestinal juice a large number of evenly distributed particles from which potassium chloride is slowly released. Thus a high local potassium chloride concentration may be avoided and removal of the pharmaceutical composition is ensured. The disadvantage of this process resides in the fact that in the manufacturing process a large amount of organic solvent (chloform/methanol) is used for the coating and the elimination thereof presents significant problems.

Problems of environmental pollution are eliminated by the use of an aqueous polymer dispersion. According to European patent application No. 52,075 potassium chloride crystals are efficiently coated by using a 2.5:1 - 5:1 mixture

consisting of an aqueous dispersion of a 70:30 mixture of ethyl acrylate and methyl methacrylate (marketed under the tradename Eudragit NE 30 D by the company Röhm) and an aqueous ethyl cellulose dispersion (marketed under the tradename Aquacoat ECD-30 by the company FMC). When coating crystals having a particle size of 0.3-0.8 mm, however, more than 25 % of the coating material is needed to obtain suitable release and this makes the preparation of the composition both complicated and expensive.

Potassium chloride compositions which meet all the up-to-date requirements are not known from prior art. The therapeutical application of potassium chloride has become more and more widespread and this requires sustained release potassium chloride compositions which can be prepared in an economical manner whereby risks of environmental pollution are eliminated.

Summary of the invention

It is the object of the present invention to provide potassium chloride compositions which meet the following requirements:

– in view of the high dose, a high active ingredient content and a low auxiliary (coating agent) content;

– sustained release effect in order to provide a long-lasting and even blood level of the active ingredient;

– multi-dosage form in order to decrease the mucosa damaging gastrointestinal side-effects, and the formation of

particles having a hydrophilic surface which are quickly distributed in the gastrointestinal juice;

– small specific surface, compact particles and a smooth surface in order to reduce the amount of the coating.

The composition according to the present invention must fulfil the following further requirements too:

– the particles of the composition should not adhere during the manufacturing procedure and use;

– the particle size distribution of the particles to be coated should be uniform;

– the particles should be of low porosity;

– the coating agent should be free of solvents damaging the environment (e.g. chlorine containing solvents).

The above objects are achieved with the aid of the composition and process of the present invention.

The essence of the present invention is a controlled active ingredient release multi-dosage pharmaceutical composition, in the form of tablets or hard gelatine capsules, having a potassium chloride content of 500-1000 mg, prepared by the so-called "pellet-formulation method" and coating.

The term "pellet" used throughout the present patent specification relates to special granules, characterized by a particle size between some tenth of mm and some mm (generally between 0.5 mm and 2.0 mm), a small deviation of the particle size, substantially spherical form, small surfacial

roughness and a particle compactness approaching that of pressed materials.

According to the present invention there is provided a controlled release multi-dosage pharmaceutical composition in solid oral form, preferably in the form of tablets or hard gelatine capsules and having a potassium chloride content of 500-1000 mg per dosage unit characterized by a content of at least 70 % by weight of potassium chloride, in the form of coated and partially uncoated pellets.

According to a further feature of the present invention there is provided a process for the preparation of controlled release multi-dosage pharmaceutical compositions comprising pellets containing at least 70 % by weight of potassium chloride, preferably in the form of tablets or hard gelatine capsules and having a potassium chloride content of 500-1000 mg per dosage unit which comprises preparing controlled active ingredient release tablets or hard gelatine capsules from pellets having a potassium chloride content of at least 70 % by weight.

Detailed description of the invention

According to a preferred embodiment of the process of the present invention tablets or hard gelatine capsules are prepared

– by blending potassium chloride with 0.1-0.5 % by weight of an anti-adhesion agent and 10-25 % by weight of microcrystalline cellulose optionally containing sodium carboxymethyl cellulose;

– converting the mixture into pellets by treatment in succession with a 15-20 % by weight aqueous potassium chloride solution, an aqueous hydrophobizing agent diluted to 0.5-5 % by weight and optionally water;

– drying said pellets;

– coating said dried pellets with a coating solution comprising an aqueous dispersion of an ethyl acrylate/methyl methacrylate copolymer and/or an ammonium methacrylate copolymer as film forming agent, a hydrophobizing agent, 5-35 % by weight of a lower alkanol, talc and optionally a dye;

– applying potassium chloride onto the surface of said coated particles;

– if desired admixing said coated particles with uncoated potassium chloride particles having the above composition and suitable auxiliary agents or a mixture thereof;

– and pressing said mixture into tablets or filling same into hard gelatine capsules.

According to a particularly preferred embodiment of the present invention the compositions are prepared by

– admixing potassium chloride with 0.1-0.3 % by weight of colloidal silica;

– grinding said mixture to particles 90 % thereof having a particle size smaller than 100 μm;

– blending said ground material with 10-25 % by weight of microcrystalline cellulose;

– wetting the mixture thus obtained in succession with 5-15 % by weight of a 20 % by weight aqueous potassium

chloride solution and 0.3-0.7 % by weight of a 1.5-2.5 % by weight aqueous dimethyl polysiloxane dispersion;

– if desired spraying water onto said mixture;

– drying the pellets thus obtained;

– separating the pellets having a particle size between 0.8 mm and 1.6 mm;

– coating said pellets with a coating liquid comprising 4-6 % by weight of a 35 % aqueous ethyl acrylate/methyl methacrylate dispersion, 5-35 % by weight of ethanol, 0.5-1.0 % by weight of talc, 0.2-1.0 % by weight of dimethyl polysiloxane and 0.01-1.0 % by weight of a dye;

– and applying onto the surface of said coated pellets 0.5-2.0 % by weight of potassium chloride by using an aqueous potassium chloride solution.

According to a preferred embodiment of the present invention there are provided oral pharmaceutical compositions preferably in tablet or hard gelatine capsule form comprising pellets which contain at least 70 % by weight of potassium chloride, 10-25 % by weight of microcrystalline cellulose, 0.1-0.5 % by weight of an anti-adhesion agent and 0.1-5.0 % by weight of a hydrophobizing agent; a coating layer applied onto said pellets comprising 3-10 % by weight of an ethyl acrylate/methyl methacrylate copolymer and/or an ammonium methacrylate copolymer, a hydrophobizing agent, talc and optionally a dye; and optionally uncoated potassium chloride particles and further auxiliary agents applied onto said layer.

According to the present invention as anti-adhesion agent substances generally used for this purpose may be applied e.g. silica, talc, magnesium stearate, preferably silicium dioxide.

As hydrophobizing agent preferably dimethyl polysiloxane, magnesium stearate, calcium stearate, hydrogenated fatty oils, particularly preferably dimethyl polysiloxane may be used.

Microcrystalline cellulose may be replaced by microcrystalline cellulose containing sodium carboxymethyl cellulose.

The main component of the composition (more than 80 % by weight) is composed of potassium chloride pellets having a particle size of 0.5-2.0 mm and coated with a coating layer which ensures the controlled release of the active ingredient. Said pellets are substantially spherical particles. In the pellets 90 % of the potassium chloride particles has a size below 100 μm; 90 % by weight of the size of the microcrystalline cellulose particles is smaller than 50 μm; the size of the colloidal silica particles is smaller than 1 μm and the dimethyl polysiloxane is used as a liquid (preferably an aqueous emulsion). The coating of the pellets comprises as film-forming agent an ethyl acrylate/methyl methacrylate copolymer and/or an ammonium methacrylate copolymer and as further auxiliary agent talc and a hydrophobizing agent, preferably dimethyl polysiloxane.

In addition to the coated pellets which ensure the controlled active ingredient release, the composition of the present invention may also comprise uncoated pellets and further auxiliary agents generally used in the preparation of oral pharmaceutical compositions (e.g. magnesium stearate, microcrystalline cellulose etc.) which facilitate the filling into hard gelatine capsules and the tabletting of the pellets.

According to prior art the active ingredient content of pellets, prepared of organic molecules which are much more easily plastifiable than inorganic salts, does not exceed 50 % by weight [see e.g. Capes, C.E.: Particle Size Enlargement, Elsevier Scientific Publ. Co., Amsterdam, (1980); Ghebre-Sellasie, I.: Pharmaceutical Pelletization Technology, Marcel Dekker Inc., N.Y. Basel, (1989)]. In the light of the above teaching of prior art it is surprising that from non-plastic potassium chloride pellets having an active ingredient content higher than 70 % by weight can be prepared. Thus the recognition of the present invention could not be aforeseen.

It has been found that the finer particles are used as starting material of the pellet manufacturing procedure, the more compact pellets having a smoother surface and a more uniform particle size distribution are obtained. For this reason the potassium chloride starting material is to be ground. Since potassium chloride is strongly susceptible to agglomeration, in order to facilitate grinding and to prevent further adhesion of the ground material one may proceed preferably by adding an anti-adhesion agent. For this purpose preferably colloidal

silica my be used (e.g. Aerosil 200; manufactured by Degussa, Germany). The amount of colloidal silica is generally 0.1-0.5 % by weight, preferably 0.1-0.2 % by weight.

The ground potassium chloride is thereafter blended in a suitable equipment with microcrystalline cellulose, having a fine particle size as well. For this purpose e.g. Avicel PH 105 (manufactured by FMC Corp.) may be used. Microcrystalline cellulose may be used per se or as a mixture formed with sodium carboxymethyl cellulose (Avicel CL-611 or Avicel RC-581). Blending may be carried out in a usual equipment (e.g. high speed kneading machine or centrifugal fluidization granulation machine). The blend is then wetted with a concentrated potassium chloride solution having a concentration of 15-25 % by weight, preferably 20 % by weight, and then further wetted with a hydrophobizing agent. As hydrophobizing agent preferably a dimethyl polysiloxane emulsion may be used, particularly a dimethyl polysiloxane emulsion diluted to 0.5-5 % by weight (Pharsil E 1049; Wacker Chemie).

The further steps of the pellet manufacturing procedure may be carried out by different methods. According to a process the wetted substance is subjected to extrusion in a suitable equipment, spheronized in another apparatus and finally dried in the third equipment. According to another process formation of the particles and drying are carried out in the original apparatus. Alternatively one may start the process

in the first apparatus and switch over to the second equipment before drying.

It is known that during the pellet manufacturing procedure a suitable moisture content must be achieved, when pellet formation begins and the growth of particle size continues, respectively.

It has been found in a surprising manner that on using a concentrated potassium chloride solution the plastifiable state (pellet formation) may be achieved with a smaller amount of liquid than in case of water and the use of a concentrated potassium chloride solution results in more compact pellets having a lower porosity, a rougher surface and a higher solidity. The mechanism of this complicated phenomenon is not clearly known. According to our best knowledge presumably the following procedure takes place. Since potassium chloride is readily soluble in water, during the pellet manufacturing procedure the water dissolves a part of potassium chloride. This dissolution procedure can not be handled and is accompanied by an uncontrollable change of the consistence of the wet particle agglomeration as time proceeds. On carrying out wetting of the granules with a saturated or nearly saturated potassium chloride solution the liquid - solid substance ratio being of fundamental importance from the point of view of pellet formation is not affected by such dissolving procedure. It is however not intended to limit the scope of protection by any theoretical thesis.

The use of water is accompanied by a further unfavourable phenomenon. On drying a solution of an uncontrollable concentration gets onto the surface, from which crystals of random size and quantity remain back. A part of such crystals may be abraded and results in a powderlike material which affects the sustained release effect of the layer in an unfavourable manner.

The amount of the crystals, which affects the smoothness of the surface of the particles and consequently the coating procedure in an unfavourable manner, is considerably smaller when using a potassium chloride solution due to the smaller amount of the liquid and the higher local concentration.

The further advantage of the use of a concentrated or nearly saturated potassium chloride solution as formulating liquid is that on drying potassium chloride crystals remain in the pores of the pellets and partially fill out the same.

It is namely essential that during pellet formulation, in the growth and spheronification phase, the pores of the growing pellets should be filled with liquid (to enable formulation). During this procedure (compacting growth, spheronification) a part of the liquid gets on the surface, but another part thereof remains in the pores of the crude (moist) particles until the beginning of the drying. This solvent is removed during drying but the place of the solvent is retained in the pellets as pore.

On using less liquid and a potassium chloride solution in the place of water more compact pellets having a higher potassium chloride content are obtained.

The concentration of the potassium chloride solution used in the process of the present invention is near to the saturated concentration at room temperature (34.0 g of potassium chloride are soluble in 100 g of water at 20°C which corresponds to a concentration of 25.37 % by weight ["Analitikai zsebkönyv"; Műszaki Könyvkiadó, Budapest, (1971)]. The concentration actually used is however somewhat lower than the above value due to technical problems (e.g. obstruction of the soldering head).

It is preferred to use a potassium chloride solution having a concentration of about 15-20 % by weight.

The present invention is based on the further recognition that silicon emulsion plays an important role in the uniform particle size distribution of the pellets and the increase of the amount of the product fraction having the desired particle size.

It has been found that in the most critical phase of the pellet forming procedure, which particle size growth often takes place very quickly i.e. explosion-like, by injecting a silicon emulsion (hydrophobizing) the procedure may be slowed down, the process can be better handled, the deviation of the particle size distribution can be decreased and the amount of the desired product fraction can be significantly increased.

In addition to the aforesaid, the use of a silicon emulsion has secondary not neglectable advantages too. The surface of the particles becomes more hydrophobic, the particles are less susceptible to stick to the wall, the surface of the particles becomes smoother and later this promotes the adhesion of the coating layer.

Drying and size fractionating of the pellets is carried out by methods known from prior art.

In the next step of the process of the present invention the pellets are coated. This coating step provides the desired slow active ingredient release kinetics.

According to one of the coating methods the active ingredient release velocity of readily soluble salts is made sustained release with the aid of a lipophilic (hydrophobic) coating layer. For this purpose a natural, semi-synthetic or synthetic fat, hardened vegetable oil, wax or wax derivatives may be used.

This process may e.g. be carried out by heating a mixture of an inorganic salt and a solid fat to a temperature above the melting point of the fat, uniformly distributing the salt in the melt, and thereafter cooling and granulating the system (e.g. German patent No. 1,948,019). According to another process the fat is dissolved in a solvent (e.g. chloroform, carbon tetrachloride) and sprayed onto the particles (e.g. Hungarian patent No. 191,202).

According to a further known coating method a polymer film is formed on the surface of the particle and thus a

sustained active ingredient release is ensured. The release velocity is determined by the diffusion speed of the active ingredient through the film.

The coating layer may be formed by dissolving the polymer in an organic solvent or a mixture of organic solvents and spraying the solution onto the surface of the particles. The dissolved chain-formed polymer particles form a loose coil structure and after drying of the film adhere to each other to yield a uniform, compact, good covering layer.

In order to protect environment there is a trend to replace the so-called "solvent coating methods" by so-called "dispersion coating procedures". For this reason manufacturers have developed their well-known and frequently used polymer film forming systems in the form of aqueous dispersions too. There is an unambiguous trend towards the use of dispersion coating materials and the quality of the coating dispersions is continuously improving. In the dispersions the polymeric particles are present in the form of small latex balls and in the course of coating these balls are linked to each other. It can be easily realized that such a coating is less compact and it is true from theoretical considerations as well that in order to achieve identical sustained release effect from the dispersion coating liquid a larger amount is to be used than from a corresponding solvent type system. Moreover there is a higher risk of the formation of so-called "orange-shell" structure coatings (see in details

Cole, G., Hogan, J., Aulton, M., "Pharmaceutical Coating Technology").

The present invention is based on the further recognition that by using a coating liquid of suitable composition the advantages of the above two systems can be combined.

According to a further feature of the present invention to a commercially available aqueous dispersion of an ethyl acrylate/methyl methacrylate copolymer and/or an ammonium methacrylate copolymer containing conventional pharmaceutical auxiliary agents (e.g. talc, dimethyl polysiloxane, optionally dyes etc.) a lower alkanol is added in an amount of 5-35 % by weight. As lower alkanol straight or branched chain alkanols having 1-3 carbon atoms may be used, preferably ethanol, isopropanol or a mixture of ethanol and isopropanol. It has been found that the addition of a lower alkanol affects the behaviour of the coating dispersion in an advantageous manner. This recognition is so much the more surprising as according to the instructions for use of the manufacturers the addition of organic solvents to dispersion coating materials is generally prohibited. On using the special water : alcohol according to the present invention the polymer is not precipitated on use, in the course of the process mainly water is evaporated and at the same time the formation and quality of the dry coating and the amount thereof is similar to that obtained by the hitherto known pure "organic solvent" procedures.

The main film forming component used according to the process of the present invention is an ethyl acrylate/methyl methacrylate copolymer and/or ammonium methacrylate copolymer known for such purposes. One may particularly preferably use an Eudragit® product marketed by the company Rohm Pharma. The following three marketed products of said firm proved to be particularly useful: dry powder or granule; solution formed with isopropanol or a mixture of isopropanol and acetone; or aqueous dispersion.

It is an object of the present invention to achieve with the aqueous dispersion coating agent an identical or similar active ingredient release as obtained with the aid of an organic solvent system. The above object is reached by adding 5-35 % by weight of a lower alkanol (preferably ethanol and/or isopropanol) to an aqueous polymer dispersion.

Under the effect of the ethanol or isopropanol, used in a relatively lower amount, the polymer forms a quasi intermediate state between the dispersion and the organic solvent systems. The appearance of the polymer is still similar to that of the dispersion (white, milky), however the behaviour thereof approaches to that of the organic solvent system. Namely, the lower alkanol (ethanol or isopropanol) partially dissolves the polymer particles being on the surface of the latex micelia, thereby facilitates the agglomeration thereof, because they get into contact on the surface of the particles to be coated.

In addition to the aforesaid ethanol and isopropanol have two further roles: on the one hand they facilitate the suspension of the difficultly wettable powders used in the coating (talc, silica) which are known to cause many technical problems in the preparation of the suspension/dispersion coating systems, while on the other they improve the spraying properties of the dispersion (smaller drops are formed, the coating layer is more uniform) because the surface tension of the aqueous system is reduced.

The pellets prepared according to the present invention possess very useful properties. The pellets are compact, have a low porosity, their surface is uniform and smooth, the particles are relatively hydrophobic, the particle size distribution interval is uniform, the specific surface is significantly more favourable than that of crystals and the coating shows the above disclosed advantages. Moreover when approximately identical amount of coating (or polymer film) is applied, from the product of the present invention a significantly lower amount of potassium chloride is released than from the known products. The results of this comparative experiment are shown in Table 1. As reference the data shown on Fig. 3 of the prospectus "INFO 2.4" of the company Rohm Pharma are used.

Table 1

Release of potassium chloride active ingredient

Polymer (% by weight)	Release of active ingredient, in %			
	Invention product		Reference product	
	2 hours	4 hours	2 hours	4 hours
5	36	81	94	100
5.5	32	75		
6	24	65	85	99
7			75	96
8			67	93

It can be seen from the above Table that the amount of the active ingredient released from the invention composition is only about 25-40 % of that released from the reference product.

The dispersion-solvent coating composition of the present invention has a further advantage being particularly significant and surprising from the point of view of the stability of the composition. After coating the film formed on the surface of the particles obtains the final properties very quickly, within some days and therefore no subsequent treatment (e.g. thermal treatment) is needed. This also means that the coating layer does not "age". According to our tests the quality of the coating layer remains unchanged for at least 3 years.

It is very important to prevent particles from adhesion both during the manufacturing process and in the stomach. According to the present invention this may be achieved by applying potassium chloride onto the coated particles, preferably by spraying thereon a saturated potassium chloride solution. Thus on the one hand the particles coated with the polymer are prevented from adhesion (otherwise the particles are susceptible to stick despite of the talc and silica added) while on the other the surface of the coated particles becomes hydrophilic, whereby the particles become readily wettable in aqueous medium (e.g. in the stomach) and do not stick to each other. The amount of potassium chloride applied onto the surface is 0.5-5.0 % by weight of the complete active ingredient content and therefore does not affect the release velocity to a considerable extent.

According to prior art for this purpose surfactants are used which may have however unfavourable and undesired properties (they effect the release and absorption of the active ingredient, cause taste problems, foam may be formed in the stomach etc.). According to this feature of the present invention the material applied onto the surface of the particles is identical with the active ingredient and the amount thereof is neglectable in comparison to that of the total active ingredient content; therefore no unfavourable effect is observed.

It appears from the aforesaid that the present invention is fundementally different from the teaching of prior art.

According to Hungarian patent No. 194,495 in order to affect release velocity the water soluble agent is incorporated into the coating of the particle (i.e. tablet core), while pursuant to US patent No. 4,295,315 a surfactant is used to prevent adhesion.

Since according to the present invention adhesion is prevented by using the active ingredient per se in the disclosed manner, the active ingredient content of the pellets is increased.

The present invention does not only relate to the preparation of a potassium chloride composition characterized by a release profile of a given type, but also provides a means to affect the release profile at any optional point of the formulation procedure.

According to a particularly preferred embodiment of the present invention the coated potassium chloride pellets are admixed at a given ratio with uncoated potassium chloride particles before further processing (i.e. prior to tabletting or encapsulation). This provides a very simple and elegant process for the preparation of pharmaceutical compositions of various release velocity, including compositions of a given type (e.g. 0 grade or primary degree release kinetics).

Further details of the present invention are to be found in the following Examples without limiting the scope of protection of the patent to said working Examples.

Example 1

Composition filled into capsules, containing coated and uncoated pellets. The preparation and coating of pellets is carried out in a laboratory centrifugal fluidization granulating equipment.

Preparatory processing of the raw material

14.97 kg of potassium chloride (pharmaceutical grade) are pre-ground in a pilot-plant high-speed granulating apparatus (type Lödige FM50.lz) for 5 minutes. After addition of 0.03 kg of Aerosil 200 the mixture is blended for 10 minutes and thereafter ground in a rod mill (Alpine 160Z type) until 90 % by weight of the product has a particle size smaller than 100 µm. This product is referred to furtheron as "potassium chloride premix".

Pellet formulation

255 g of the above potassium chloride premix are blended with 45 g of Avicel PH 105 in a laboratory centrifugal fluidization granulator. The mixture is granulated in succession with 150 g of a 20 % by weight potassium chloride solution, 50 g of a silicon emulsion diluted with distilled water to 2 % by weight (E2 type; dry substance content 35 %; manufacturer Wacker Chemie) and about 35 g of distilled water and converted into pellets. The wet pellets are dried in the same equipment and the product is sieved on a 0.8 and 1.6 mm sieve. Thus about 150-200 g of pellets having a particle size of 0.8-1.6 mm are obtained (referred to furtheron as "pellet core"). This pellet manufacturing step is repeated at

least 3 times. In the pellet coating step only the pellet core fraction is used (particle size between 0.8 and 1.6 mm).

Coating of pellets

400 g of pellet cores are coated with 180 g of a coating dispersion in a laboratory centrifugal fluidization granulating equipment in a manner known from prior art. The coating dispersion is prepared as follows:

In 38.21 g of distilled water 0.03 g of a dye (Ariavit indigocarmine) is dissolved. To the solution 18.00 g of 96 % ethanol are added, whereupon in succession 3.20 g of talc, 42.37 g of distilled water, 6.17 g of a 35 % silicon emulsion and 72.00 g of a 30 % Eudragit NE 30 D dispersion are added.

After application of the polymer dispersion 38.2 g of a 20 % by weight potassium chloride solution are applied onto the surface of the coated particles.

Release of the coated pellets

Test method: 750 mg of coated pellets in 900 ml of 37°C distilled water; release measuring apparatus corresponding to USP having a rotating basket; chloride determination with silver nitrate titration; potentiometric end point detection.

1 hour : 11 %; 2 hours : 27 %; 4 hours : 52 %;
6 hours : 72 %; 8 hours : 85 %.

Pellet blending

Coated pellets and pellet cores are blended in a 82:18 ratio, thereafter 750 mg portions of the blend are filled into capsules.

Release results

Test method: see above except that one capsule each is tested.

1 hour :	30 %;	2 hours :	43 %;	4 hours :	64 %;
6 hours :	79 %;	8 hours :	89 %,	10 hours :	95 %.

Example 2

Composition filled into capsules, containing coated and uncoated pellets. Preparation and coating of the pellets is carried out in a pilot plant centrifugal fluidization granulating equipment.

Preparatory processing of the raw material

The potassium chloride premix is prepared as described in Example 1.

Pellet formulation

7703.9 g of a potassium chloride premix are blended with 1359.5 g of Avicel PH 105, the blend is granulated in a pilot-plant centrifugal fluidization granulator in succession with 4531.8 g of a 20 % by weight potassium chloride solution, 1510.5 g of a silicon emulsion (E2 type, dry substance content 35 %, manufacturer Wacker Chemie) diluted with distilled water to 2 % by weight and 266-925 g of distilled water. Pellets are formed. The wet pellets are dried in the same equipment and the product is sieved on a 0.8 and 1.6 mm

sieve. As a result of pellet production 6-7 kg of particles having a particle size between 0.8 and 1.6 mm are obtained (referred to furtheron as "pellet core"). This pellet production process is repeated at least twice. For the coating step only the pellet core fraction (particle size between 0.8 and 1.6 mm) is used.

Coating of pellets

10 kg of pellet cores are coated with 4887 g of a coating dispersion in a pilot-plant centrifugal fluidization granulator (Glatt GPCH 5 type) in a manner described in prior art. The coating dispersion is prepared as follows: 1 g of a dye (Ariavit indigocarmine) is dissolved in 500 g of distilled water, the solution is admixed with 488.69 g of 96 % ethanol, whereupon in succession 86.99 of talc, 1000 g of distilled water, 167.55 g of a 35 % silicon oil emulsion, 1954.75 g of a 30 % Eudragit NE 30 D dispersion are added and the mixture is filled up to 4887 g with distilled water.

After application of the polymer dispersion 955 g of a 20 % by weight potassium chloride solution are applied onto the surface of the coated particles.

Release results of the coated pellet

Test method: see above

1 hour :	1 %;	2 hours :	4 %;	4 hours :	31 %;
6 hours :	50 %;	8 hours :	68 %.		

Pellet blending

In order to achieve the desired release rate coated pellets and pellet cores are blended in a ratio of 80:20 and the mixture is filled into capsules in portions of 750 mg.

Release of the pellet blend

Test method: see in Example 1.

1 hour :	20 %;	2 hours :	25 %;	4 hours :	43 %;
6 hours :	58 %;	8 hours :	71 %;	10 hours:	81 %.

Example 3

Composition filled into capsules, containing coated and uncoated pellets. The preparation and coating of pellets is carried out in an industrial centrifugal fluidization granulating equipment.

Preparatory processing of the raw material

174.65 kg of pharmaceutical grade potassium chloride are pre-ground in a plant high-speed granulating equipment (Diosna A400 type) for 5 minutes. After addition of 0.35 kg of Aerosil 200 the mixture is blended for 10 minutes. The blend is ground in a rod mill (Alpine type) until 90 % of the product has a particle size smaller than 100 µm. (This product is referred to furtheron as "potassium chloride premix".)

Pellet formulation

85 kg of the potassium chloride premix are blended with 15 kg of Avicel PH 105, the blend is granulated in a plant centrifugal fluidization granulator (type Glatt GPCG 200) in succession with 50 kg of a 20 % by weight potassium chloride solution, 16.6 kg of a Pharsil E 1049 silicon emulsion diluted

to 2 % by weight and about 10 kg of distilled water. Pellets are formed. The wet pellets are dried in the same equipment and the product is sieved on a 0.8 and 1.6 mm sieve. In the pellet manufacturing process about 60-70 kg of pellets having a particle size of 0.8-1.6 mm are obtained (referred to furtheron as "pellet core"). The pellet manufacturing step is repeated at least 3 times. For the coating step only the pellet core fraction (particle size between 0.8 and 1.6 mm) is used.

Pellet coating

175 kg of pellet cores are coated with 105 kg of a coating dispersion in the plant size centrifugal fluidization granulator (type Glatt GPCG 200) in a manner described in prior art. The coating dispersion is prepared as follows: 20.8 g of a dye (Ariavit indigocarmine) are dissolved in 36 kg of distilled water. The solution is admixed with 10.27 kg of 96 % ethanol, whereupon in succession 1.84 kg of talc, 3.18 kg of a 39 % silicon emulsion, 2 kg of distilled water and 41.38 kg of a 30 % Eudragit NE 30 D dispersion are added. The mixture is filled up with distilled water to 105 kg.

After application of the polymer dispersion 16.7 kg of a 20 % by weight potassium chloride solution are applied onto the surface of the coated particles.

Release results of the coated pellets

The test method described in Example 1 is used.

1 hour : 2 %; 2 hours : 24 %; 4 hours : 65 %; 6 hours : 84 %.

Pellet blending

Coated pellets and pellet cores are blended in a ratio of 87:13 in order to reach the desired release rate. 750 mg portions of the blend are filled into capsules.

Release results of the pellet blend

The test method is described in Example 1.

1 hour : 18 %; 2 hours : 35 %; 4 hours : 67 %;
6 hours : 86 %; 8 hours : 94 %.

Example 4

Composition filled into capsules. The pellets are prepared in a laboratory extruder and spheronizer, dried in a laboratory fluidization granulating and drying equipment and coated in a laboratory vessel.

Preparatory processing of the raw materials

The potassium chloride premix is prepared as described in Example 1.

Pellet formulation

11.12 kg of potassium chloride premix are blended with 1.20 kg of Avicel PH 105 and 0.60 kg of Avicel CL 611 in a pharmaceutical high speed granulator (type Lödige FMZ50.Iz). The mixture is wetted and kneaded with 2.40 kg of a 20 % by weight potassium chloride solution and a silicon emulsion (type E2, manufacturer: Wacker Chemie) diluted with 0.54 kg of distilled water to 3.5 % by weight in several portions. The wet mass is added into a pilot plant roller extruder (type Schüter PP85) with the aid of a screw feeder and subjected to extrusion.

2 kg of the extruded filaments are placed into a pilot plant spheronizer (diameter 300 mm; type RM300; fluted disk) and spheronized at about 800 rpm. 4000 g of the spherical particles obtained are dried in a laboratory fluidization granulating and drying apparatus. From the dried product the 1.2-1.6 mm fraction is separated by manual sieving and used in the coating step.

Pellet coating

1800 g of pellet cores are coated with 1670 g of coating dispersion in a laboratory vessel in a known manner. The dispersion is prepared as follows:

0.333 g of a dye (Ariavit indigocarmine) are dissolved in 520.5 g of distilled water, whereupon 7.26 g of a SE 2 type silicon emulsion and 20.04 g of Cirtoflex 2 are added. In a separate vessel 1.67 g of Aerosil 972 are admixed with 103.54 g of micronized talc and 150.0 g of 96 % ethanol are added. This mixture and 98.657 g of distilled water are added to the first solution. To the homogenous solution thus obtained 601.20 g of Eudragit RS30D, 66.80 g of Eudragit RL30D dispersion and 100 g of distilled water are added.

750 mg portions of the coated pellet are filled into capsules.

Release results of the encapsulated coated pellet

The test method described in Example 1 is used.

1 hour : 22 %; 2 hours : 43 %; 4 hours : 71 %; 6 hours : 92 %.

Example 5

Composition filled into capsules, containing pellets. The pellets are prepared in a laboratory "high speed" mixer and coated in a laboratory centrifugal fluidization granulating equipment.

Preparatory processing of the raw material

The potassium chloride premix is prepared as described in Example 1.

Pellet formulation

913.25 g of a potassium chloride premix are blended with 150 g of Avicel PH 105. The mixture is granulated with 183.75 g of a 20 % by weight potassium chloride solution, 76.75 g of a silicon emulsion diluted to 4.34 % by weight and about 40 g of distilled water in a laboratory pharmaceutical high speed mixer (type Zanchetta Roto-Junior). Pellets are formed. The wet granules are dried in the same equipment and the product is sieved on a 0.8 and 1.6 mm sieve. Thus 600 g of 0.8-1.6 mm pellet cores are obtained. This fraction (0.8-1.6 mm) is used in the coating step.

Pellet coating

400 g of pellet core are coated as described in Example 1.

750 mg portions of the coated pellet are filled into capsules.

Example 6

Tablet composition comprising coated pellets. The pellets are prepared in a laboratory extruder and spheronizer,

dried in a laboratory fluidization granulating and drying equipment and coated in a laboratory vessel.

Preparatory processing of the raw material

The potassium chloride premix is prepared as described in Example 1.

Pellet formulation

12.75 kg of potassium chloride premix are blended with 1.50 kg of Avicel PH 105 and 0.75 kg of Avicel CL 611, the mixture is wetted and kneaded with 2.75 kg of a 20 % by weight potassium chloride solution and a silicon emulsion diluted with 0.63 kg to 3.5 % by weight in a high speed granulating equipment (type Lödige FM50.lz) in several portions. The wet mass is added with the aid of a screw feeder into a pilot plant extruder (type Schlüter PP85) and extruded. 2 kg of the extruded filaments are placed into a pilot plant spheronizer (type Schlüter RM300; diameter 300 mm; fluted disk) and spheronized at 800 rpm. 4000 g of the spherical particles are dried in a laboratory fluidization granulating and drying equipment. The 1.2-1.6 mm fractions are separated from the dried product by manual sieving and the 1.2-1.6 mm fraction thus obtained is used for the coating step.

Pellet coating

1850 g of pellet core are coated with 1670 g of a coating dispersion in a laboratory fluidization granulating, drying and coating equipment in a known manner. The coating dispersion is prepared as follows: 0.333 g of a dye

(Ariavit indigocarmine) are dissolved in 520.5 g of distilled water. To the solution 14.52 g of a SE 2 type silicon emulsion are added. In a separate vessel 1.67 g of Aerosil 972 and 103.54 g of micronized talc are admixed, 150.0 g of 96 % ethanol are added, whereupon the mixture thus obtained and 111.437 g of distilled water are added to the first solution. To the homogenous solution thus obtained 668.00 g of Eudragit NE 30D dispersion and 100 g of distilled water are added.

Tabletting of pellets

Coated pellets and Avicel PH 102 are blended in a ratio of 70:30 and from the mixture thus obtained tablets weighing 1.3 g and having a diameter of 15 mm are pressed.

What we claim is,

1. Controlled release multi-dosage pharmaceutical composition in solid oral form, preferably in the form of tablets or hard gelatine capsules and having a potassium chloride content of 500-1000 mg per dosage unit characterized by a content of at least 70 % by weight of potassium chloride, in the form of coated and partially uncoated pellets.

2. Tablets and hard gelatine capsules according to Claim 1 comprising pellets which contain at least 70 % by weight of potassium chloride, 10-25 % by weight of microcrystalline cellulose, 0.1-0.5 % by weight of an anti-adhesion agent and 0.1-5.0 % by weight of a hydrophobizing agent; a coating layer applied onto said pellets comprising 3-10 % by weight of an ethyl acrylate/methyl methacrylate copolymer and/or an ammonium methacrylate copolymer, a hydrophobizing agent, talc and optionally a dye; and optionally uncoated potassium chloride particles and further auxiliary agents applied onto said layer.

3. Composition according to Claim 2 comprising colloidal silica as anti-adhesion agent.

4. Composition according to Claim 2 comprising dimethyl polysiloxane as hydrophobizing agent.

5. Composition according to any of Claims 2-4 wherein the coated particles contain above the polyacrylate coating 0.5-5.0 % by weight of potassium chloride related to the total weight of the composition.

6. Composition according to any of Claims 2-5 wherein the microcrystalline cellulose contains sodium carboxymethyl cellulose.

7. Composition according to any of Claims 2-6 wherein the coated and uncoated particles contain 75-90 % by weight of potassium chloride, 13.5-24.8 % by weight of microcrystalline cellulose, 0.1-0.5 % by weight of colloidal silica and 0.1-5.0 % by weight of dimethyl polysiloxane.

8. Composition according to any of Claims 2-7 wherein the coating contains 2-10 % by weight of an ethyl acrylate/methyl methacrylate copolymer, 0.2-2.0 % by weight of talc and 0.1 -5.0 % by weight of dimethyl polysiloxane.

9. Composition according to any of Claims 2-8 comprising 2.3-13 % by weight of coating related to the total weight of the particles.

10. Composition according to any of Claims 2-9 comprising particles having a diameter of 0.5-2.0 mm.

11. Process for the preparation of the composition according to Claim 1 which comprises preparing controlled release tablets or hard gelatine capsules from pellets containing at least 70 % by weight of potassium chloride.

12. Process according to Claim 11 which comprises

– blending potassium chloride with 0.1-0.5 % by weight of an anti-adhesion agent and 10-25 % by weight of microcrystalline cellulose optionally containing sodium carboxymethyl cellulose;

– converting the mixture into pellets by treatment in succession with a 15-20 % by weight aqueous potassium chloride solution, an aqueous hydrophobizing agent diluted to 0.5-5 % by weight and optionally water;

– drying said pellets;

– coating said dried pellets with a coating solution comprising an aqueous dispersion of an ethyl acrylate/methyl methacrylate copolymer and/or an ammonium methacrylate copolymer as film forming agent, a hydrophobizing agent, 5-35 % by weight of a lower alkanol, talc and optionally a dye;

– applying potassium chloride onto the surface of said coated particles;

– if desired admixing said coated particles with uncoated potassium chloride particles having the above composition and suitable auxiliary agents or a mixture thereof;

– and pressing said mixture into tablets or filling same into hard gelatine capsules.

13. Process according to Claim 12 which comprises using colloidal silica an anti-adhesion agent.

14. Process according to Claim 12 which comprises using dimethyl polysiloxane as hydrophobizing agent.

15. Process according to any of Claims 12-14 which comprises grinding the mixture of potassium chloride and the anti-adhesion agent to an extent whereby 90 % by weight of the ground product has a particle size below 100 μm.

16. Process according to Claim 12 which comprises using ethanol, isopropanol or a mixture thereof by the preparation of the coating solution.

17. Process according to Claim 12 which comprises applying an aqueous potassium chloride solution to the surface of the coated pellets, preferably by spraying.

18. Process according to Claim 12 which comprises using microcrystalline cellulose or lactose as auxiliary agent when admixing the coated and uncoated pellets.

19. Process according to Claim 12 which comprises

– admixing potassium chloride with 0.1-0.3 % by weight of colloidal silica;

– grinding said mixture to particles 90 % thereof having a particle size smaller than 100 μm;

– blending said ground material with 10-25 % by weight of microcrystalline cellulose;

– wetting the mixture thus obtained in succession with 5-15 % by weight of a 20 % by weight aqueous potassium chloride solution, 0.3-0.7 % by weight of a 1.5-2.5 % by weight aqueous dimethyl polysiloxane dispersion;

– if desired spraying water onto said mixture;

– drying the pellets thus obtained;

– separating the pellets having a particle size between 0.8 mm and 1.6 mm;

– coating said pellets with a coating liquid comprising 4-6 % by weight of a 35 % aqueous ethyl acrylate/methyl methacrylate dispersion, 5-35 % by weight of

ethanol, 0.5-1.0 % by weight of talc, 0.2-1.0 % by weight of dimethyl polysiloxane and 0.01-1.0 % by weight of a dye;

– and applying onto the surface of said coated pellets 0.5-2.0 % by weight of potassium chloride by using an aqueous potassium chloride solution.

20. Process according to Claim 19 which comprises wetting the blend in a centrifugal fluidization granulator.

21. Process according to Claim 19 which comprises carrying out the process in a fluidization apparatus equipped with a rotating plate.

22. Process according to Claim 12 or 19 which comprises forming the pellets in an extruder spheronizer.

23. Process according to Claim 12 or 19 which comprises carrying out pellet formation in a high speed kneading machine.

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(57) Abstract

The invention relates to controlled release multi–dosage pharmaceutical composition in solid oral form, preferably in the form of tablets or hard gelatine capsules and having a potassium chloride content of 500–1000 mg per dosage unit characterized by a content of at least 70 % by weight of potassium chloride, in the form of coated or partially uncoated pellets. The tablets or hard gelatine capsules according to the present invention are comprising pellets which contain at least 70 % by weight of potassium chloride, 10–25 % by weight of microcrystalline cellulose, 0.1–0.5 % by weight of an anti–adhesion agent and 0.1–5.0 % by weight of a hydrophobizing agent; a coating layer applied onto said pellets comprising 3–10 % by weight of an ethyl acrylate/methyl methacrylate copolymer and/or an ammonium methacrylate copolymer, a hydrophobizing agent, talc and optionally a dye; and optionally potassium chloride particles and further auxiliary agents applied onto said layer.

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 397 574 A (CHEN CHIH-MING) 14 March 1995 (1995-03-14) column 1, line 7 - column 1, line 13; example 1 ---	1-11
X	THOMA, K. ET AL: "Preparation and testing of potassium chloride diffusion pellets" PHARM. IND. (1989), 51(6), 685-9 , XP002116009	1-11
Y	paragraph 2 of Section 2.6, Section 4 table 1 ---	12-23
Y	GB 2 087 235 A (CIBA GEIGY AG) 26 May 1982 (1982-05-26) page 1, line 37 - page 1, line 41 page 2, line 14 - page 2, line 19; examples 1-3 --- -/--	12-23

[X] Further documents are listed in the continuation of box C.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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